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ケースレポート

A DEATH CASE IN WHICH THE VICTIM WAS RUN OVER AFTER INTAKE OF PSYCHOPHARMACEUTICAL DRUGS INCLUDING CARBAMAZEPINE

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カルバマゼピンを含む向精神薬服用後に自動車に轢過された交通事故死の一例

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Summary

A curious case, in which a 60-year old male was run over and killed after intake of psychopharmaceuticals including carbamazepine, is presented. By forensic autopsy, the cause of his death was judged to be an injury of the pons. The concentrations of carbamazepine in whole blood and urine were found to be 8.55 and 2.76 μg/ml, respectively. He seemed to have lain down on the road under drowsy state due to the intake of carbamazepine and flunitrazepam, just before the traffic accident.

Key words: Traffic accident; Run over; Carbamazepine; Flunitrazepam; Gas chromatography (GC); Nitrogen-phosphorus detection (NPD); Solid-phase extraction

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Introduction

Forensic toxicologists frequently experience run-over accidents where victims lie down on roads after alcohol intake. In this report, we present a rare case in which the intake of psychopharmaceutical drugs including carbamazepine could contribute to lying down of the victim on a road and resulted in a traffic accident.

Case history

A 60-year old man was diagnosed as manic disorder in May 1995 and treated with psychopharmaceuticals. His manic symptoms were improved in 1997 and the prescription for him was 3 mg of bromperidol, 3 mg of biperiden chloride, 600 mg of carbamazepine and 1 mg of flunitrazepam per day at that time. However, he became hyperkinetic at night. On March 20, 1997, he was said to have taken 200 mg of carbamazepine and 1 mg of flunitrazepam around 21:30 and went out of home soon after oral administration of the drugs. He was run over by a car around 22:30.

Autopsy findings

The body was 155 cm high, and weighed 33 kg. Abrasions were mainly found in the head, face and neck. On internal examination, fractures were found as follows: complicated fractures in facial bones, severe fractures of cranial fossae, and multiple fractures of both ribs, which were severer in the left. In the brain, a severe contusion of the pons and a slight subarachnoidal haemorrhage in both sides of the cerebrum were found. Contusions in the liver and left lung, and subcutaneous and intramuscular haemorrhage in the wide regions of the left back were also observed. The severe contusion of the pons was judged to be the cause of his death.

Toxicological analyses

Materials

Carbamazepine was purchased from Sigma (St. Louis, MO, USA). Mianserin (internal standard, IS) was obtained from Organon (Oss, Netherlands); flunitrazepam from Hoffmann-La Roche Ltd. (Basel, Swtzerland). Other chemicals used were of analytical grade. Sep-Pak C_{18} cartridges were purchased from Waters Associates (Milford, MA, USA).

Methods

Gas chromatography (GC) analyses for carbamazepine were carried out on an HP 5890 Series II gas chromatograph with nitrogen-phosphorus detection (NPD) (Hewlett-Packard Co.,

Wilmington, DE, USA) with an Rtx®-5 Amine fused silica capillary column (30 m×0.32 mm i.d., film thickness: 1.0 μm) purcased from Restek Co. (Bellefonte, PA, USA). GC conditions were: column temperature, 100 to 280℃ (1 min hold at 100 ℃ and 20 ℃/min); injection temperature, 230 ℃; detector temperature, 280℃; helium flow rate, 3 ml/min.

GC analyses for flunitrazepam were carried out on a Shimadzu GC-14B gas chromatograph with electron capture detection (ECD) (Shimadzu Corp., Kyoto) with a DB-17 fused silica capillary column (30 m×0.32 mm i.d., film thickness: 0.25 μm) purchased from J & W Scientific (Folsom, CA, USA). The GC conditions for ECD were the same as those for GC-NPD, except for injection temperature, 270℃ and detector temperature, 300℃. The samples were injected in the splitless mode and the splitter was opened after 1 min.

Mass spectra in the positive ion electron impact (PIEI) mode were measured on a JMS-DX505H mass spectrometer (JEOL, Tokyo) with an HP-5890 Series II gas chromatograph (Hewlett-Packard Co., Wilmington, DE, USA). The MS conditions were: accelerating voltage, 3.0 kV; ionization current, 300 μA; separator temperature, 280 ℃; ionization temperature, 280 ℃; and electron energy, 70 eV. GC conditions for GC/mass spectrometry (MS) were the same as those described for GC-NPD.

Carbamazepine, mianserin (IS) and flunitrazepam in body fluids were extracted according to the previous report by solid-phase extraction method [1] with slight modifications. Drugs extracted from body fluids were dissolved in 50 μl of methanol, and 1 μl of it was subjected to GC analyses.

Results and discussion

The EI-mass spectra of the extracts from blood and urine showed peaks at m/z 236 (molecular peak), 193 and 165, which were almost identical to that of the authentic carbamazepine. After identification of the drug in the samples and confirmation of no contamination by impurities in the drug peaks by GC/MS, we quantitated carbamazepine in whole blood and urine samples using GC-NPD. Figure 1 shows gas chromatograms of the authentic carbamazepine (100 ng on-column) and IS (20 ng on-column), and of drugs extracted from the whole blood and urine samples of the deceased. The retention times of carbamazepine and IS were 16.4 and 14.9 min, respectively. The concentrations of carbamazepine in the whole blood and urine samples were 8.55 and 2.76 μg/ml, respectively. We tried to detect flunitrazepam using GC-ECD, but failed to detect it from the body fluids, probably because of its low therapeutical dose.

The most controversial point in this case is the reason why this man lay down on the road. Four drugs, carbamazepine, flunitrazepam, bromperidol and biperiden were prescribed for the

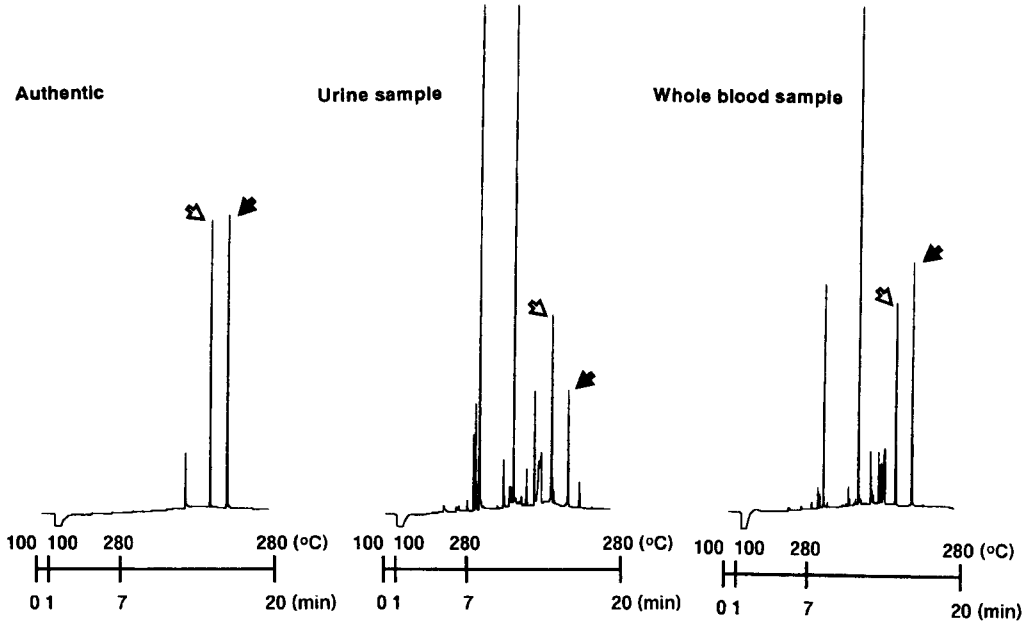

Fig. 1. Capillary GC-NPD for the authentic carbamazepine (filled arrow) and mianserin (IS, open arrow) and for extracts of urine and whole blood samples of the deceased. The amounts of the authentic carbamazepine and IS were 100 ng and 20 ng on-column, respectively. One microgram of IS was added to 0.5 ml of the urine or whole blood sample and extracted with Sep-Pak C_{18} cartridges.

treatment of his mania; he was said to have taken 200 mg cabamazepine and 1 mg of flunitrazepam about 1 h before the accident. Since we failed to detect flunitrazepam, we focused on quantitating carbamazepine. During long-term therapy of carbamazepine, untoward effects including drowsiness, vertigo, ataxia, diplopia and blurred vision could happen [2]. Therapeutic concentrations of carbamazepine are reported to 6 to 12 [2] or 4 to 12 [3] μg/ml in plasma. The carbamazepine concentration in whole blood in this case is not toxic, but could result in the drowsy state together with the effect of flunitrazepam. Such accidents often happen after alcohol intake, but this kind of case with psychopharmaceuticals seems rare and merits being reported.

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